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10/510,625	04/20/2005	Nava Zisapel	2007-120	9296

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EXAMINER	
PHILLIPS JR, WELDON P	

ART UNIT	PAPER NUMBER
4121	

NOTIFICATION DATE	DELIVERY MODE
04/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/510,625	ZISAPEL, NAVA	
	Examiner	Art Unit	
	WELDON PHILLIPS JR.	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-47* is/are pending in the application.

4a) Of the above claim(s) *38-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/08/2004 & 12/14/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application for patent entered the national stage under 35 U.S.C. 371 on April 20, 2005 from PCT/IL03/00240, filed March 20, 2003, which claims benefit from Israel Patent Application 149377, filed April 8, 2002.

Receipt is acknowledged of applicant's claim for priority under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Status

Claims 29-47, as amended on October 8, 2004, are pending.

Election/Restrictions

Applicant's election of Group II in the reply filed on March 27, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the group restriction requirement, this portion of the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election of the species zolpidem in the reply filed on March 27, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the species election requirement, this portion of the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 38-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or

linking claim. Election was made **without** specifying traverse in the reply filed on March 27, 2009.

Acknowledgement

Copies of the International Search Report and International Preliminary Report on Patentability have been received/obtained by the examiner and their contents have been considered.

Information Disclosure Statement

Two Information Disclosure Statements (IDS) were timely filed by applicant on October 8, 2004 and December 14, 2006 in compliance with 37 CFR § 1.97, 37 CFR § 1.98 and MPEP § 609. All references cited on both IDS were considered by the examiner.

Claim Rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 which forms the basis for the rejections under this section as set forth in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 29 and 34-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Bersani (Prog. Neuro-Psychopharmacol. & Biol. Psychiat. Vol. 24, 185-191 (2000), see PTO-892).

As to claim 29, the Bersani reference teaches the addition of a 10:30 PM oral dosage of 3 mg melatonin to the normal pharmaceutical regimen of eleven manic patients with treatment-resistant insomnia incompletely responding to usual hypnotic therapies and sleeping only for an average of only 2.43 hours/night (abstract; p. 187, para. 2; p. 188, para. 5 and Figure 1). Bersani teaches that the normal regimen of two of the eleven patients included 10 mg/day zolpidem, among other drugs (p. 187, Table 1, Patients #4 and #8). Bersani further teaches that all patients, which necessarily includes the two taking zolpidem, showed a significantly longer sleep duration after 30 days of treatment with 3 mg melatonin + normal regimen when compared with their normal regimen in the absence of melatonin.

Although there was an absence of an explicit definition of a "hypnotic effect" in applicant's specification, Merriam-Webster's definition of hypnotic provided some guidance, ie: "tending to produce sleep" (http://www.merriam-webster.com/dictionary/hypnotic). Since Bersani teaches the administration of melatonin to two patients who experienced an increase in sleep duration, Bersani has taught the potentiation of a hypnotic effect in a patient in need thereof. The examiner is aware that other pharmaceuticals were given to these patients as part of their normal pharmaceutical regimens. However, claim 29 uses "comprising" language, which

allows for the presence of other steps in the method, which in this case allows for other pharmaceutical agents to be administered. As such, claim 29 is anticipated by Bersani.

As to claims 34-37, said at least one compound, e.g., zolpidem, inherently comprises a bicyclic fused ring system, reading on claim 34, inherently includes at least two ring nitrogen atoms, reading on claim 35, inherently comprises a imidazo[1,2,-a]pyridine skeleton, reading on at least one of the optional bicyclic ring systems of claim 36, and was zolpidem, reading on at least one of the optional compounds of claim 37. As such, claims 34-37 is anticipated by Bersani.

Claims 29 and 34-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Suhner (Aviation, Space and Environmental Medicine Vol. 72, 638-646 (2001), see IDS dated December 14, 2006).

As to claim 29, the Suhner reference teaches that jet-lag is particularly severe in passengers traveling eastward through several time zones (p. 638, col. 1, para. 1), such that this population of patients approaches this problem by utilizing hypnotics and resynchronizing their internal clocks through the use of melatonin (p. 638, col. 1, para. 1). The Suhner reference teaches the co-administration of 5 mg melatonin and 10 mg zolpidem to transcontinental passengers returning to Switzerland on overnight flights from the American continent after spending one to six weeks in the Americas and passing through six to nine time zones on the return trip (p. 639, col. 1, para. 4 and col. 2, para. 1). Thus, the Suhner reference teaches the administration of melatonin and a

non-barbiturate and non-benzodiazepine hypnotic compounds, e.g., zolpidem, to eastbound transcontinental passengers crossing six to nine timezones, a patient population known to suffer from jet-lag and known to be a population in need thereof. Passengers took melatonin and zolpidem during a specified interval of time during the return flight and on each of the next 4 nights upon their return (p. 639, col.. 2, para 1). A number of data points over the 5 treatment days showed a potentiated hypnotic effect in a patient in need thereof in the melatonin + zolpidem cohort vs. the zolpidem cohort: sleep latency on night 3 at home, number of awakenings on night 2 at home, and wakeful periods after sleep onset on days 1, 2 and 4 at home (p. 642, Table II), each of which are commonly used as measures of a hypnotic effect, as discussed supra. As such, claim 29 is anticipated by the Suhner reference.

As to claims 34-37, said at least one compound, e.g., zolpidem, inherently comprises a bicyclic fused ring system, reading on claim 34, inherently includes at least two ring nitrogen atoms, reading on claim 35, inherently comprises a imidazo[1,2,-a]pyridine skeleton, reading on at least one of the optional bicyclic ring systems of claim 36, and was zolpidem, reading on at least one of the optional compounds of claim 37. As such, claims 34-37 are anticipated by the Suhner reference.

Claim Rejections – 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suhner (Aviation, Space and Environmental Medicine Vol. 72, 638-646 (2001) in view of Ohkawa (USPN 6,348,485, see PTO-892).

As discussed supra, the Suhner reference teaches the co-administration of melatonin and zolpidem to transcontinental passengers returning to Switzerland on

overnight flights from the American continent. The Suhner reference does not teach that melatonin and zolpidem are administered in a single pharmaceutical formulation. The Ohkawa reference teaches this shortcoming.

The Ohkawa patent teaches that the combination of active compounds, which in the Ohkawa patent comprise (*S*)-N-[2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-b]furan-8-yl)ethyl]propionamide (Compound A), a melatonin agonist known in the art, and zolpidem, could be provided as a single pharmaceutical formulation/dosage form or as separate dosage forms, such as tablets, fine granules, capsules and granules (col. 3, line 15 and col. 10, line 49), reading on the limitation of claim 30. Several of the optional limitations of claim 31 are taught either explicitly or inherently by the references including, e.g., zolpidem is inherently (a) a $GABA_A$ receptor modulator, (b) with a fused-ring system containing ring nitrogen and (e) a non-barbiturate and non-benzodiazepine hypnotic, as well as the explicit teaching by Ohkawa of (d) unit dosage forms containing the combination of active compounds and the recitation in claim 1 of Ohkawa that (f) the hypnotic zolpidem, when administered in combination with Compound A, is present in subtherapeutic doses if melatonin were not administered (col. 11, line 14).

The motivation to combine the Ohkawa patent with the Suhner reference lies in the teaching by the Ohkawa patent of methods for increasing the effects and allowing for a reduction in the dose of certain hypnotics, e.g., zolpidem, thereby potentially reducing the side effects associated with said hypnotic, e.g., zolpidem (col. 2, line 15), such as recoil insomnia, dysmnesia, ataxia after awakening from sleep and somnolescence (col. 4, line 42). As such, it would have been obvious to one skilled in

the art at the time the invention was made to use the drug combination taught by the Suhner, e.g., melatonin + zolpidem, in the single pharmaceutical formulations taught by the Ohkawa patent to create the invention of claims 30 and 31, because one would expect a benefit from reducing the dose of a hypnotic like zolpidem that, despite its successes in the marketplace, is still recognized to have significant side effects for its users. As such, claims 30 and 31 are obvious over Suhner in view of Ohkawa.

Claims 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suhner in view of Ohkawa, as applied to claims 30 and 31 above, and further in view of Richardson (USPN 6,042,849, see PTO-892).

As discussed supra, the Suhner reference teaches the co-administration of melatonin and zolpidem to transcontinental passengers returning to Switzerland on overnight flights from the American continent. As discussed supra, the Ohkawa patent teaches a method for potentiating the hypnotic effect of hypnotic, e.g., zolpidem, through co-administration of Compound A, a melatonin agonist, and a non-barbiturate and non-benzodiazepine compound, e.g., zolpidem, in a single unit dosage form. The Ohkawa patent further teaches that the pharmaceutical formulation containing Compound A, which as discussed supra may also comprise zolpidem, may be formulated for sustained-release, but does not teach that the single unit dosage form of Compound A and zolpidem may be formulated for sustained release of melatonin and regular release of zolpidem. The Richardson patent addresses this shortcoming.

The Richardson patent teaches a dual layer tablet comprising an immediate release layer that disintegrates in the stomach to provide access to the components

thereof and a controlled release layer that remains intact until reaching the intestine where it dissolves providing access to its components including 3 mg melatonin (col. 8, lines 42-65 and col. 10, Table III). Applicant describes the dissolution of the outer layer of its two-layer tablet to be immediate (p. 14 of the specification), therefore the term "immediate release layer" is interpreted to read on "regular release" found in claim 33. As used in the Richardson patent, the terms "controlled" and "sustained" are equivalent (col. 5, line 29), therefore meeting the sustained release limitation of claim 32. The Richardson patent teaches that said dual layer tablet comprises a Eudragit acrylic polymer enteric acid resistant coating on the controlled release layer of the tablet which does not dissolve until reaching the more alkaline environment of the upper small intestine (col. 8, lines 55-61 and col. 11, lines 25-33).

The motivation to combine the Richardson patent with the Suhner reference lies in the teaching by Richardson that melatonin containing formulations are particularly useful in persons with reduced melatonin levels (col. 4, line 12). As such, it would have been obvious to one skilled in the art at the time the invention was made to use the drug combination taught by the Suhner reference in the dual layer tablet taught by the Richardson patent to create the invention of claims 32 and 33, since the release profile of a controlled release formulation of melatonin is known to more closely mirror physiological melatonin changes as suggested by Suhner (p. 644, col. 1, para. 3). As such, claims 32 and 33 are obvious over Suhner in view of Ohkawa and further in view of Richardson.

Claims 29-31 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohkawa (USPN 6,348,485, see PTO-892).

Page 20 of the applicant's instant specification recites:

> "While particular embodiments of the invention have been particularly described hereinabove, it will be appreciated that the present invention is not limited thereto, since as will be readily apparent to skilled persons, many variations and modifications can be made. **Such variations and modifications which have not been detailed herein are deemed to be obvious equivalents of the present invention. For example, structural analogs of melatonin which substantially imitate the function of melatonin in the human body are deemed to be obvious chemical equivalents of melatonin.** The essential concept, spirit and scope of the present invention will be better understood in the light of the claims which follow (emphasis added)."

As to claims 29-31, the Ohkawa patent teaches a method of treating a mammal with the combination of (*S*)-N-[2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-b]furan-8-yl)ethyl]propionamide (Compound A), a structurally similar melatonin agonist known in the art, and zolpidem for the treatment of sleep disorders, among them primary insomnia and sleep-awake rhythm disorders including work-shift syndrome and timezone syndrome also known as jet-lag (col. 10, line 44). According to applicant's above admission, melatonin and its structural analog Compound A, a melatonin receptor agonist, are obvious chemical equivalents. Therefore, Compound A could be used in the invention according to Ohkawa or melatonin could be substituted for Compound A according to the invention as disclosed by Ohkawa (col. 2, line 9). Among mammals, humans are the first species the Ohkawa patent recites as the subjects for effective treatment with Compound A + hypnotic, e.g., zolpidem (col. 11, line 11). More specifically, claim 1 of the Ohkawa patent recites the administration of subtherapeutic doses (ineffective for inducing sleep) of Compound A, an obvious chemical equivalent of melatonin, and subtherapeutic doses (ineffective for inducing sleep) of a second

compound, e.g., zolpidem, such that the combination induces sleep, reading on potentiating the hypnotic effect (col. 11, line 14). Such a combination would be advantageous, in that reducing the doses of the hypnotic agent would be expected to reduce the hypnotic agent's associated and problematic side effects, such as rebound insomnia, dysmnesia, ataxia after awaking from sleep and somnolescence (col. 4, line 42). As such, based on the substitution of melatonin for Compound A, claim 29 is obvious over Ohkawa.

The Ohkawa patent teaches that the combination of active compounds could be provided as a single dosage form or as separate dosage forms, such as tablets, fine granules, capsules and granules (col. 3, line 15 and col. 10, line 49), reading on the limitation of claim 30. Based on the teachings above, the Ohkawa patent explicitly or inherently teaches several of the optional limitations of claim 31, including, e.g., zolpidem is inherently (a) a $GABA_A$ receptor modulator, (b) with a fused-ring system containing ring nitrogen and (e) a non-barbiturate and non-benzodiazepine hypnotic, among others such as the explicit teaching of (d) unit dosage forms containing the combination of active compounds and the recitation in claim 1 that (f) the hypnotic zolpidem, when administered in combination with Compound A, is present in subtherapeutic doses (if given alone), as discussed supra. As such, claims 30 and 31 are obvious over Ohkawa.

As to claims 34-37, said at least one compound, e.g., zolpidem, inherently comprises a bicyclic fused ring system, reading on claim 34, inherently includes at least two ring nitrogen atoms, reading on claim 35, inherently comprises a imidazo[1,2,-

a]pyridine skeleton, reading on at least one of the optional bicyclic ring systems of claim 36, and was zolpidem, reading on at least one of the optional compounds of claim 37. As such, claims 34-37 are obvious over Ohkawa.

Claims 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohkawa, as applied to claims 29-31 and 34-37 above, in view of Richardson (USPN 6,042,849, see PTO-892).

As discussed supra, the Ohkawa patent teaches a method for potentiating the hypnotic effect of zolpidem through co-administration of melatonin agonist Compound A and a non-barbiturate and non-benzodiazepine compound, e.g., zolpidem, in a single unit dosage form. The Ohkawa patent further teaches that the pharmaceutical formulation containing the melatonin agonist Compound A, which as discussed supra may also comprise zolpidem, may be formulated for sustained-release, but does not teach that the single unit dosage form of melatonin agonist Compound A and zolpidem may be formulated for sustained release of melatonin agonist Compound A and regular release of zolpidem. The Richardson patent addresses this shortcoming.

The Richardson patent teaches a dual layer tablet comprising an immediate release layer that disintegrates in the stomach to provide access to the components thereof and a controlled release layer that remains intact until reaching the intestine where it dissolves providing access to its components including 3 mg melatonin (col. 8, lines 42-65 and col. 10, Table III). Applicant describes the dissolution of the outer layer of its two-layer tablet to be immediate (p. 14 of the specification), therefore the Richardson's "immediate release layer" is interpreted to read on "regular release" found

in claim 33. As used in the Richardson patent, the terms "controlled" and "sustained" are equivalent (col. 5, line 29), therefore meeting the sustained release limitation of claim 32. The Richardson patent teaches that said dual layer tablet comprises a Eudragit acrylic polymer enteric acid resistant coating on the controlled release layer of the tablet which does not dissolve until reaching the more alkaline environment of the upper small intestine (col. 8, lines 55-61 and col. 11, lines 25-33).

The motivation to combine the Richardson patent with the Ohkawa patent lies in the teaching by Richardson that melatonin containing formulations are particularly useful in persons with reduced melatonin levels (col. 4, line 12). As such, it would have been obvious to one skilled in the art at the time the invention was made to use the drug combination taught by the Ohkawa patent in the dual layer tablet taught by the Richardson patent to create the invention of claims 32 and 33, since the release profile of a controlled release formulation of melatonin is known to more closely mirror physiological melatonin levels.

Claim Disposition

Claims 29-37 are rejected at this time. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to WELDON PHILLIPS JR. whose telephone number is (571)-270-7673. The examiner can normally be reached Monday through Thursday &

every other Friday between 7:30 AM and 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/WP/
Examiner, Art Unit 4121

/Patrick J. Nolan/
Supervisory Patent Examiner, Art Unit 4121